REMARKS

Claims 1-15 and 18-28 are pending. Claims 9-15 and 18-28 are withdrawn from consideration as being drawn to non-elected inventions. Claim 6 is withdrawn from consideration as being drawn to a non-elected species. The withdrawn claims are not canceled as Applicant understands that they are entitled to claims drawn to non-elected species upon allowance of a generic claim. Claims 16-17 were previously canceled. With this Amendment, Claim 1 is amended. Thus, after entry of this Amendment, Claims 1-5, 7 and 8 are under consideration. The amendments of the claims and the various rejections raised in the Office Action are discussed in more detail below.

The Amendments of the Claims

Claim 1 is amended for clarity and the scope of the claim is unchanged. The amendment of Claim 1 is presented at this time in response to the new rejections under 35 U.S.C. §§ 102(b) and 103(a). Applicant respectfully asserts that the amendment to Claim 1 places the claims in better form for consideration on appeal. Support for the amendment to Claim 1 is found in Claim 7 as originally filed and in paragraphs 60 and 202 of the instant application which was published January 5, 2006 as U.S. Patent Application Publication No. 2006/0003329 A1. No new matter is added by virtue of the amendment.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 2, and 7 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by International Application Publication No. WO 99/27087 ("Morrissey *et al.*" or "Hybridon"). Specifically, the Patent Office alleges that Morrissey *et al.* disclose: (1) antisense molecules that bind to the CDK4 gene and inhibit expression of the CDK4 protein; (2) methods of identifying other antisense molecules that inhibit CDK4 expression; and (3) methods of treating a mammal afflicted with a tumor associated with aberrant CDK4 expression. (Office Action, p. 3). Based on these allegations, the Patent Office concludes that the antisense molecules of Morrissey *et al.* suppress CDK4 protein expression, which disrupts a non-kinase function mediated by CDK4 and, therefore, anticipate the claimed invention. (*Id*, p. 3). Applicant traverses the rejection.

The standard for anticipation under 35 U.S.C. § 102(b) is set forth in M.P.E.P. § 2131: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)." In addition, "[t]he identical invention must be

shown in as complete detail as is contained in the. . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In view of the above standard, Morrissey *et al.* can not anticipate the claimed invention because Morrissey *et al.* do not expressly or inherently disclose each and every element of the claimed methods. Morrissey *et al.* relate to compounds that inhibit CDK4 expression in U87 cells (*see, e.g.*, p. 12, line 23 to page 13, line 4, and Figures 4 and 5). As a result, the compounds of Morrissey *et al.* would inhibit all of the functions of CDK4, including its kinase and CKI sequestrating activity. Therefore, Morrissey *et al.* do not expressly or inherently disclose an agent likely to disrupt a function, other than kinase and a CKI sequestrating activity, of a critical normal gene product.

For at least these reasons, Morrissey *et al.* do not expressly or inherently disclose and, therefore, can not anticipate the methods of independent Claim 1 and dependent Claims 2 and 7. Accordingly, Applicant respectfully requests that the rejection of Claims 1, 2, and 7 under 35 U.S.C. § 102(b) be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1, 2, and 7 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,962,316 ("Beach *et al.*") in view of Haas *et al.* "Mutual requirement of CDK4 and Myc in malignant transformation: evidence for cyclin D1/CDK4 and $p16^{INK4A}$ as upstream regulators of Myc," Oncogene 1997 Jul 10;15(2):179-92 ("Haas *et al.*"). Specifically, the Patent Office alleges that Beach *et al.* disclose: (1) "a method for generating peptide or non-peptide agents based on the structure of a 16 kDa cell-cycle regulatory protein (CCR) that are able to compete for binding with CDK4; (2) "the identification of potential peptidyl fragments of CDK4 that can competitively bind to the 16 kDa CCR and interfere with its ability to bind CDK4"; and (3) that the "16 kDa CCR protein. . . is cyclin-dependent kinase inhibitor 2A ($p16^{INK4a}$)". (Office Action, p. 4). The Patent Office acknowledges that Beach *et al.* do "not disclose that the inhibition of the binding of $p16^{INK4a}$ to CDK4 would disrupt a non-kinase function mediated by CDK4[.]" (*Id.*). To provide this missing element, the Patent Office alleges that Haas *et al.* disclose: (1) "that a catalytically inactive CDK4, that can still bind to $p16^{INK4a}$, cooperates with activated H-ras in transforming cells"; (2) "CDK4 mutants that can not bind to $p16^{INK4a}$, but are still catalytically active, can no longer transform cells." (*Id.*). Based on these allegations that Patent Office concludes that "binding of CDK4 with $p16^{INK4a}$ and not the kinase activity of CDK4 is critical for transforming cells with CDK4" and "[i]nhibitors that abrogate the binding of CDK4 with $p16^{INK4a}$ would disrupt a non-kinase function mediated by CDK4." (*Id.*). Applicant traverses the rejection.

The Patent Office bears the initial burden of establishing a case of *prima facie* obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1998); MPEP § 2142. If the Patent Office does not establish a *prima facie* case, the Applicants are under no obligation to submit evidence of non-obviousness, and the rejection must be withdrawn. *Id.*

Applicant respectfully asserts that the disclosures by Beach *et al.* and Haas *et al.* of methods of decreasing the binding of $p16^{INK4A}$ to CDK4 are irrelevant to the claimed invention because $p16^{INK4A}$/CDK4 binding is not a claimed function mediated by a critical normal gene product. For example, paragraphs 199 and 200 of U.S. 2006/0003329 disclose that the CDK4 protein is a critical normal gene product. However, paragraphs 200 and 202 state that the claimed function of the CDK4 gene product in the division and survival of cancer cells is not related to CDK4's normal activities, such as, binding to $p16^{INK4A}$:

> **[0202]** The applicant has identified a critical normal function of the CDK4 gene product in cancer cells. It appears that CDK4 acts to elevate CDK1, p9Ka and possibly CDK2, CDK6 and p27 by a mechanism that is independent of its role in the cell cycle. The region of CDK4 protein that mediates this function is unknown. CDK4 protein has many known functional regions with regard to its action in normal cells (see **FIG. 3**). These involve regions responsible for binding to. . . $p16^{INK4}$[.] The novel function of CDK4 in clinical cancer cells described here does not involve the known functions of the regions described above.

Therefore, CDK4 binding to $p16^{INK4A}$ is not a claimed function mediated by a critical normal gene product.

In view of the above, Applicant respectfully asserts that the disclosures of Beach *et al.* and Haas *et al.* are irrelevant to the claimed invention and Applicant respectfully requests the rejection of Claims 1, 2, and 7 under 35 U.S.C. § 103(a) in view of Beach *et al.* and Haas *et al.* be withdrawn.

Claims 3, 4, and 5 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Beach *et al.* in view of Haas *et al.* and further in view of International Application Publication No. WO 99/42821 ("Warenius *et al.*" or "Theryte"). The Patent Office alleges that "[n]either Beach *et al.* or Haas *et al.* disclose a cancer cell sample that consists of cells in which the CDK1 and CDK4 gene products are both elevated as compared with control cells in which the ratio of the levels of the CDK1 and CDK4 gene products is in the range of 0.6 to 1.6." (Office Action, p. 5). The Patent Office further alleges that Warenius *et al.* disclose "that CDK1 and CDK4 proteins are elevated in cancer cells (Figs. 3 and 4) and that the ration [sic] of CDK4 to CDK1 is approximately 1 (Fig. 5)." (*Id.*). The Patent Office

concludes that the skilled artisan would have been motivated to apply the teaching of Warenius *et al.* of the diagnostic value of CDK1 and CDK4 levels in cancer to the drug screening methods of Beach *et al.* and Haas *et al.* because Warenius *et al.* allegedly state that the increased levels of CDK1 and CDK4 in cancers may be used in drug screening of compounds specifically toxic to cancer tissues, which thereby renders the claimed invention obvious. (*Id.*). Applicant traverses the rejection.

As stated above, Beach *et al.* and Haas *et al.* are irrelevant to the claimed invention. Therefore, the rejection of Claims 3-5 over Beach *et al.*, Haas *et al.*, and Warenius *et al.* is improper and Applicant respectfully requests that it be withdrawn.

Claim 8 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Beach *et al.* in view of Haas *et al.* as applied to Claims 1 and 2, above, and in further view of Ceha *et al.* "Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein," Biochem Biophys Res Commun. 1998 Aug 19;249(2):550-5 (Ceha *et al.*). The Patent Office alleges that neither Beach *et al.* or Haas *et al.* disclose amino acids 172-285 of the human CDK4 gene product as mediating a function required for successful division and continued cell survival. (Office Action, p. 6). To provide this missing element, the Patent Office alleges that Ceha *et al.* disclose that amino acids 209-211 and 281-283 of CDK4 are involved in the binding of $p16^{INK4A}$ to CDK4. Therefore, the Patent Office concludes that it would have been obvious to combine Beach *et al.* and Haas *et al.* with Ceha *et al.* to identify agents that disrupt the binding of $p16^{INK4A}$ to CDK4. Applicant traverses the rejection.

As previously stated, CDK4 binding to $p16^{INK4A}$ is not a claimed function mediated by a critical normal gene product. Therefore, the teachings of Beach *et al.*, Haas *et al.*, and Ceha *et al.* are irrelevant to the claimed invention and Applicant respectfully requests that the rejection of Claim 8 be withdrawn.

Conclusion

Claims 1-15 and 18-28 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

No fees are believed to be due in connection with this Amendment. However, the Director is authorized to charge any fees that may be required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 376956-002US (368521))**.

Respectfully submitted,

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Daniel M. Becker
Reg. No. 38,376

DECHERT LLP
Customer No. 37509
Telephone: 650.813.4800
Facsimile: 650.813.4848